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Systemic acquired resistance

Jean-Pierre Métraux*, Christiane Nawrath & Thierry Genoud
*Département de Biologie, Université de Fribourg, Rte A.Gockel 3, 1700 Fribourg, Switzerland; (*author for correspondence: e-mail: jean-pierre.metraux@unifr.ch)*

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Summary

Plants can be induced to switch on defense reactions to a broad range of pathogens as a result of prior exposure to pathogens or to various chemicals or physical stress. Induced resistance is expressed locally, at the site of the infection or systemically, at sites remotely located from the initial infection. Upon recognition of the initial stimulus by the plant, a signal transduction pathway is set in motion, that includes intra and intercellular signals, and results in the activation of defense mechanisms, mostly by expression of new genes. This brief review will focus on some of the recent advances in the understanding of systemic acquired resistance and on the role played by salicylic acid in this process.
Abbreviations: BABA – β-aminobutyric acid; CWE – cell wall extract; Eth – ethylene; HR – hypersensitive reaction; ISR – induced systemic resistance; JA – jasmonic acid; PDF – plant defensin; PR – pathogenesis-related; SA – salicylic acid; SAR – systemic acquired resistance; TGA – a class of basic-region leucine zipper leucine transcription factor

Introduction

The defense of plants to pathogens comprises constitutive barriers present in plants prior to any contact with pathogens or herbivores. Furthermore, exposure to various microorganisms or other forms of stress can lead to the activation of defense mechanisms. Induced resistance depends on the recognition of a pathogen or stress by the plant. This generates a cascade of events, eventually leading to the expression of defense mechanisms, which include physical barriers, metabolites and proteins that interfere with the spread of the invading microorganism. The recognition process can vary in specificity. For instance, in its most extreme form, plants can distinguish subspecies or races of pathogenic organisms. In this case, a corresponding product of a resistance gene in the plant recognizes the product of an avirulence gene of a pathogen, a so-called race-specific elicitor; this results in a race-specific induction of resistance mechanisms. This form of induced resistance is described by the gene-for-gene hypothesis. The same conceptual framework of this hypothesis has been used to explain the situation where a broader resistance is induced in response to several races of a pathogen or even to several species (review by Mitchell-Olds & Bergelson, 2000). Generally, the speed of recognition and ensuing induction of resistance are key determinants in the success of resistance. Disease will occur if the pathogen is faster than the induced response, if no elicitors are produced or if suppressors prevent the plant defense reactions. Induced resistance may be expressed locally in the infected parts as well as in the uninfected parts of the plant. In this case, the initial recognition event also leads to the production of an endogenous systemically translocated signal that has the virtue to activate resistance mechanisms in parts of the plant remotely located from the initial site of interaction. This form of induced resistance is referred to as systemic acquired resistance (SAR) (Sticher et al., 1997; Hunt & Ryals, 1996) or systemic induced resistance (ISR) (Pieterse & Van Loon, 1999). Here, we will briefly review some salient features of SAR.

SAR induced by preinfection with pathogens

The phenomenon

The potential of plants to induce local and systemic defense responses was described several decades ago by Carbone & Arnaudi (1930), Chester (1933) and Gäumann (1946). These observations emphasized the ability of plants to become resistant after an initial infection. The term systemic acquired resistance (SAR) was first coined by Ross to describe induced resistance in the upper leaves of tobacco plants which had developed necrotic lesions on the lower leaves after inoculation with tobacco mosaic virus (TMV) (Ross, 1966). Kuc and his coworkers have extensively described SAR in cucumber and documented the broad spectrum of SAR. These studies made it clear that SAR was independent of the nature of the initial inoculant (Madamanchi & Kuc, 1991). These observations have lead to a large number of studies, and SAR has been described in over 30 plant species belonging both to di- and monocotyledonous plant families (Sticher et al., 1997).

Resistance mechanisms activated during SAR

During SAR, resistance reactions taking place in the non-infected parts of the pretreated plants can be studied separately from reactions occurring at the infection site. At the site of attack, the resistance responses of the host includes modifications of the cell wall (Hammerschmidt, 1999a), production of phytoalexins (Hammerschmidt, 1999b), synthesis of pathogenesis-related (PR) proteins (Hunt & Ryals, 1996; Van Loon, 1997; Van Loon & Van Strien, 1999), or activation of programmed cell death also called the hypersensitive reaction (HR) (Gilchrist, 1998; Grant & Mansfield, 1999; Lamb & Dixon, 1997, Richfield et al., 1998). HR is mostly associated with specific recognition of an avirulent pathogen by the host during a gene-for-gene interaction (Bonas & Van den Ackerveken, 1999; Ellis et al., 2000; Hammond-Kosack & Jones, 1997). Interestingly, despite its acknowledged role as an induced defense mechanism, the HR might also be an important component of compatible plant pathogen interactions. For example, it was shown recently that *Arabidopsis* mutants impaired in the HR response show an increased resistance to virulent strains of *Pseudomonas syringae* (Stone et al., 2000). At the systemic level, the production of PRs before a challenge infection is the most commonly observed reaction. A microscopic form of the HR dispersed throughout the systemic uninfected leaves has also been described (Alvarez et al., 1998). In contrast, other reactions such as changes in cell wall lignification were detected after challenge infection of the upper leaf but with faster induction kinetics (reviewed in Sticher et al., 1997). Thus, the systemic signal can also prepare the systemic tissue to a faster defense response; a phenomenon referred to as conditioning. Conditioning of the upper leaves by the systemic signal has been studied using a reduced system that consists of cultured cells in which pathogen attack is mimicked by a treatment with elicitors. Pretreatments with salicylic acid (SA), a possible signal for SAR (see below) or functionally related inducers such as 2,6-dichloroisonicotinic acid (INA) or benzothiadiazole (BTH; BION), potentiate elicitor-induced H_2O_2 generation or expression of defense-related genes such as *phenylalanine ammonia-lyase* (*PAL*) or *4-coumarate:CoA ligase*. Such studies where also carried out on organs or whole plants (Conrath et al., 2000; Katz et al., 1998; Kauss et al., 1999; Thulke & Conrath, 1998). Using these systems, experiments can now be aimed at the action of the systemic signal in conditioning of defense in systemic leaves. The non-protein amino acid β-aminobutyric acid (BABA) was recently shown to potentiate pathogen-specific plant resistance mechanisms and to protect *Arabidopsis* against different virulent pathogens (Zimmerli et al., 2000). BABA remains effective against *P. parasitica* in transgenic plants or mutants impaired in the SA, jasmonic acid (JA), and ethylene signaling pathways. In particular, BABA-mediated papilla formation after *P. parasitica* infection is independent of the SAR signaling pathway. BABA protects mutants insensitive to JA and ethylene against pathogenic bacteria, but was not effective in plants impaired in the SAR transduction pathway.

The signal for SAR

SA has been proposed to be the signal for induced resistance. This is based on the protective action of SA, the kinetics of accumulation after infection and various experimental evidences, including the overexpression of a bacterial salicylate hydroxylase in transgenic plants that effectively reduces the level of endogenous SA (Delaney et al., 1994; Gaffney et al., 1993, review by Sticher et al., 1997). Grafting experiments in tobacco as well as leaf excision experiments in cucumber support the notion that SA is not the primary mobile signal exported from the infected leaf

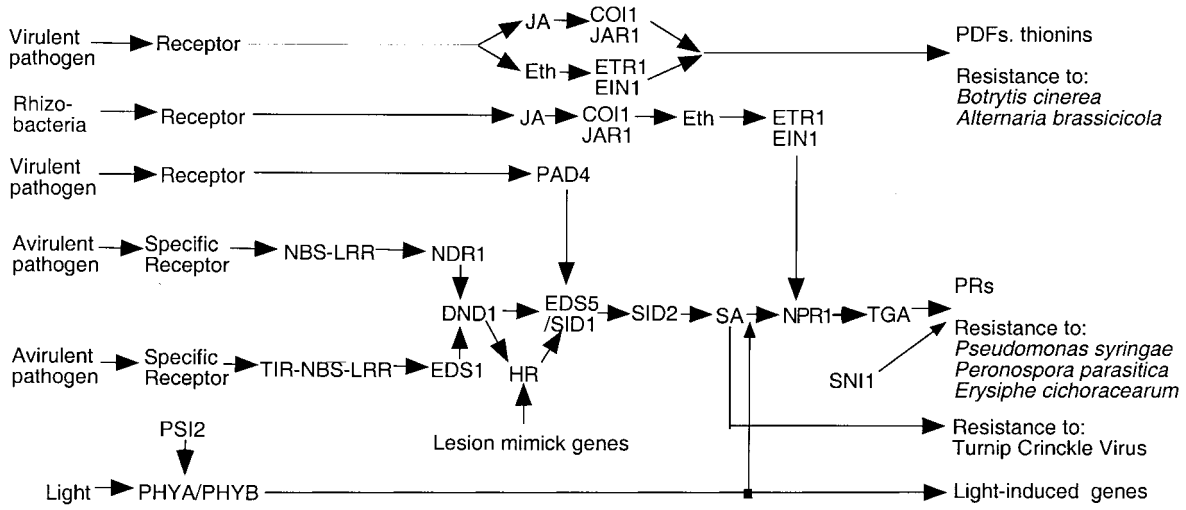

Figure 1. Schematic and simplified diagram of the signal transduction network operating in SAR. In this diagram arrows represent a flow of the information and proteins are ordered with respect to the sequence from incoming signals (left side) to the responses (right side). Abbreviations: COI: coronatine insensitive; DND: defense no death; EDS: enhanced disease susceptibility; ETR: ethylene resistant; EIN; ethylene insensitive; JAR: jasmonate resistant; NBS-LRR: nucleotide-binding site leucine-rich-repeat protein; NPR: non-expresser of PR genes; NDR: non-race-specific disease resistance; PAD: phytoalexin deficient; PHY: phytochrome; PSI: phytochrome signalling; SID: salicilic acid induction deficient; SNI: suppressor of *npr1*-inducible; TGA: basic leucine zipper (bZIP) transcription factor; TIR-NBS-LRR: Toll-interleukin-receptor nucleotide-binding-site leucine-rich-repeat protein.

to other parts of the plant (Rasmussen et al., 1991; Vernooij et al., 1994). However, transport experiments in tobacco and cucumber have shown that SA moves from its production site in the infected leaf to the upper leaves by the phloem (Shulaev et al., 1995; Mölders et al., 1996). When the overexpression of a salicylate hydroxylase is targeted to the phloem tissue of tobacco, SAR is strongly decreased, supporting a direct role of SA in systemic signaling (Mur et al., 2000). Interestingly, in tobacco, volatile methyl salicylate (MeSA) is produced from SA after infection and can induce defense by conversion to SA (Shulaev et al., 1997, Seskar et al., 1998). MeSA was proposed to be additive to SA for *in planta* signaling and to act as a signal for *inter planta* communication. Thus, it is likely that SA as well as other systemic signals could be involved in SAR.

The network of signaling

The pathway of induced resistance was extensively studied in *A. thaliana*, where a large number of mutants are available that are impaired in various steps of induced resistance (Glazebrook, 1999). Figure 1 is a schematic representation of the signal transduction pathway after pathogen attack. Different pathways are recruited upon interaction with avirulent pathogens, they depend at least on two classes of leucine-rich-repeats proteins (LRRs). These pathways eventually converge at the DND1 (defense no death) protein which controls the formation of HR cell death (Clough et al., 2000). The signaling pathway induced after certain virulent pathogens involves PAD4, a lipase domain-containing protein, that controls the production of the phytoalexin camalexin (Jirage et al., 1999). Further down the pathway, the signaling cascade depends on the EDS5/SID1 and SID2 proteins that are involved in the control of SA production (Nawrath & Métraux, 1999). The *eds5/sid1* gene has recently been cloned. It encodes a protein with several membrane-spanning and a coil domain at the N-terminus. EDS5/SID1 shows homology to the *E. coli* DNA-damage inducible DinF, a protein closely associated with the SOS-response of bacteria. The SOS response is induced upon exposure to stress or to DNA-damaging treatments. The expression of the *EDS5/SID1* gene after pathogen attack is independent of SA. It will be interesting to learn what the biochemical function of EDS5/SID1 is and how this relates to the regulation of SA levels after pathogen

attack or stress exposure (Nawrath et al., submitted for publication).

Crosstalk or interference occurs between signaling pathways (Genoud & Métraux, 1999). For example, the induction of PR-1 and the resistance to *P. syringae* show a strong dependency on light in Arabidopsis. The *phyA* and *phyB* light receptor mutants or the double mutants *phyA/phyB* are strongly impaired in SA-induced PR-1 and resistance. Light seems to enhance the sensitivity of the tissue to its own SA rather than stimulate SA production and the light pathway connects to the SA pathway downstream of SA accumulation (Figure 1) (Genoud and Métraux, unpublished results). Studies are under way to identify the elements integrating the signals from the light and the SA pathways.

The mode of action of SA

The search for a SA-binding protein has lead to catalase and ascorbate peroxidase (Durner & Klessig, 1995). The binding of SA to such enzymes might lead to the formation of a phenolic radical that in turn is involved in lipid peroxidation. The products of lipid peroxidation can activate defense gene expression (Farmer et al., 1998). Whether such radicals form sufficient lipid peroxides at the right time and place for the defense response to be induced remains to be shown. SA-binding proteins (SAPs) different from catalase were identified that show a higher affinity for SA and related functional analogues (Du & Klessig, 1997). The biological importance of these SAPs remains to be determined, but they certainly offer exciting perspectives toward an understanding of the mode of action of SA.

The induction of gene transcription by SA was also followed closely. An SA- and pathogen-inducible protein kinase (SIPK) belonging to the MAP kinase family was identified in tobacco (Zhang & Klessig, 1997). A number of studies have concentrated on the upstream regulatory sequences (URS) of the *PR-1* gene promoter, one of the culminating responses in SAR. A consensus sequence (TGACG) in the URS of *PR-1* is recognized specifically by TGA transcription factors of the bZIP protein family (Lebel et al., 1998). TGAs were also found to interact with the NPR1 protein, providing a direct link between NPR1 and SA-induced *PR-1* expression (Després et al., 2000; Zhang et al., 1999; Zhou et al., 2000). SNI1, a negative regulator of SAR represses *PR* gene expression, presumably by direct binding to a specific DNA sequence or via a transcription factor (Li et al., 1999). Other reports have identified an SA- and pathogen-inducible WRKY DNA-binding factor. This factor specifically recognizes the elicitor response element of the tobacco class I chitinase promoter. Protein phosphorylation is important for the activity of WRKY DNA-binding factors; this emphasizes the role played by kinases in SA-signaling (Yang et al., 1999).

Alternative pathways for the induction of systemic resistance

A number of studies support the existence of SA-independent pathways for the induction of defense genes and resistance. In *Arabidopsis*, the thionin 2.1 gene is inducible by methyl jasmonate, silver nitrate and pathogenic fungi but not by SA or ethephon (an ethylene-releasing compound) (Epple et al., 1995). Inoculation of *Arabidopsis* with an avirulent strain of *Alternaria brassicae* results in the accumulation of the antifungal protein plant defensin PDF1.2. Using ethylene- or JA insensitive mutants (Feys et al., 1994; Guzman & Ecker, 1990), *npr* mutants (Cao et al., 1994) or *NahG* plants expressing constitutively a bacterial gene (*NahG*) for SA degradation (Gaffney et al., 1993), it was shown that PDF1.2 expression in the leaves is independent of SA, in contrast to the PR-1 expression that depends on SA (Penninckx et al., 1996). A mutant constitutively expressing PRs (*cpr5)* was crossed with *npr1* or with *NahG* plants. The resulting homozygous lines were susceptible to the virulent bacterium *Pseudomonas syringae* pv *maculicola* ES4326 without PR-1 expression indicating that *cpr5* acts upstream of SA (Bowling et al., 1997). However, *cpr5/npr1* plants are resistant to the fungal pathogen *Peronospora parasitica* Noco2 and express elevated levels of PDF1.2. Both a *npr1*-dependent and a *npr1*-independent SAR pathway can therefore mediate resistance.

In tobacco, resistance can be induced locally and systemically with culture filtrates from the pathogenic bacterium *Erwinia carotovora* subsp. *carotovora* against the same organism. The induction depends on the activity of pectic enzymes and cellulase and takes place equally well in *NahG* plants as in controls (Vidal et al., 1997). Similarly, SA produced in response to the rhizobacterial strain of *Serratia marcescens* 90-166 was not found to be the primary determinant of induced systemic resistance in tobacco and cucumber (Press et al., 1997). The roles of SA-dependent and SA-independent signal transduction

pathway were studied in *Arabidopsis thaliana* treated with by bacterial cell-wall-degrading enzymes (CWE) (Norman-Setterblad et al., 2000). CWE triggered systemic resistance in *A. thaliana* to *Erwinia carotovora* in the same way as a pretreatment with *E. carotovora*. Using marker genes for the ethylene- and JA-signal transduction pathways (hevein-like protein and basic chitinase for ethylene, plant defensin for JA) and mutants blocked respectively in the ethylene and JA pathway, it was shown that CWE-induced activation of these marker genes depends both on ethylene and JA. CWE do not induce SA-dependent genes such as PR-1. However, SA was found to have a dual role: it enhanced the expression of the genes that depend both on ethylene and JA and inhibited the expression of a gene (vegetative storage protein acid phosphatase) that solely depends on JA (Norman-Setterblad et al., 2000). This represents an interesting case of crosstalk that shows the role of SA as a potentiator of JA- and ethylene-dependent defense responses.

Besides SAR induced by a preinfection with pathogens, different forms of induced systemic resistance were observed that are triggered by plant growth-promoting rhizobacteria (PGPRs) known from biocontrol studies. Generally, PGPRs are able to control plant pathogens by antibiotic effects, site occupancy or competition for iron through siderophores. In addition, PGPRs can also induce systemic defenses in the plants against foliar pathogens. Arabidopsis inoculated with *Pseudomonas fluorescens* exhibit SA-independent systemic protection against foliar pathogens (Pieterse et al., 1996). This was termed 'induced systemic resistance' (ISR) to distinguish this particular form of systemic resistance from pathogen-induced SAR (Pieterse et al., 1999). Interestingly, whereas ISR operates independently of PR proteins against *P. syringae,* the NPR1 protein from the SAR pathway is still necessary (Pieterse et al., 1998). In contrast, SA-dependent resistance of Arabidopsis to a viral pathogen was shown to be independent of *NPR1*, a key component in the SA signaling pathway (Kachroo et al., 2000). Enhanced levels of protection can be obtained by combining pathogen induced SAR and rhizobacteria-induced ISR (Van Wees et al., 2000). All these examples indicate that several different signaling pathways operate, that may share the same components but are connected differently.

Conclusions

Much progress has been achieved in the study of SAR. An increasing number of new elements in the signal transduction pathway has been discovered and this number will undoubtedly rise further with the advent of large-scale investigations of gene expression. From such surveys, and it becomes apparent that a high level of coordination takes place in response to signals involved in induction of resistance mechanisms such as SA, JA and ethylene (Reymond et al., 2000; Schenk et al., 2000). The signal transduction involved in the regulation of the SAR response turns out to be far from a linear chain of events and looks more and more like a network. This is perhaps the major change in paradigm this field has witnessed in the last years. It is now clear that several pathways interact, leading to defense responses targeted at various pathogens. Understanding and representing the structure of the SAR signaling network becomes a challenging task. It will require new biological investigations and, most likely, collaborations between biologists and informaticians. We have proposed the use of boolean networks as a reductionistic approach to apprehend the complexity of signaling systems (Genoud & Métraux, 1999). The logical structure of such a network integrates the properties of individual pathways as well as the emerging features arising when these pathways are studied as a whole. Individual boolean elements or combinations of elements represent effector proteins involved in the network.

From a practical point of view, it appears that the overexpression of defense-related genes for the protection of crop plants remains an interesting goal. Considering the structure of the defense network, it might be more promising to overexpress genes of effectors that control several sets of defense genes in the network. This might provide a broader resistance than overexpression of a single resistance protein. An example of such an approach has been recently provided by the overexpression of the NIM1 protein (Cao & Dong, 1998; Friedrich et al., 2000, submitted for publication).

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